I. SYNTHESIS OF COMPOUNDS IN THE β-CARBOLINE SERIES

II. POLYPHOSPHORIC ACID AS A DEHYDRATING AGENT IN ORGANIC CHEMISTRY

BY

FRANK XAVIER WERBER

B.S., Queens College, 1944
M.S., University of Illinois, 1947

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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I. SYNTHESIS OF COMPOUNDS IN THE β-CARBOLINE SERIES

Introduction

The amino acid tryptophan has long been regarded as the biogenetic precursor of a variety of alkaloids containing the β-carboline nucleus, and it has been a principal raw material for laboratory syntheses of substances containing this heterocyclic system. Until the development of a useful synthesis of *dl*-tryptophan (1), however, all the derivatives of β-carboline were comparatively rare materials, because of the scarcity of the natural alkaloids themselves and because of the difficulty in obtaining the natural amino acid, *l*-tryptophan, from protein hydrolysates. The present ready availability of *dl*-tryptophan makes it possible to produce various β-carboline compounds in sufficient quantity for detailed study, with regard to both chemical and pharmacological properties.

Discussion Of Results

The amino-β-carboline obtained by amination of β-carboline with sodamide (2) has been shown to be 1-amino-β-carboline by an independent synthesis *via* the sequence: *dl*-tryptophan, 1-methyl-β-carboline, 1-styryl-β-carboline, 1-carboxy-β-carboline, 1-carbomethoxy-β-carboline, β-carboline-1-carbonyl hydrazide, β-carboline-1-carbonyl azide, ethyl β-carboline-1-carbamate, 1-amino- β-carboline. The last compound forms a diacetyl rather than a monoacetyl derivative under mild acetylation conditions, but studies to determine the position of the second acetyl group remain incomplete.

The cyclodehydration of some β-aryl-α-acylaminopropionic acids has been examined. In each case cyclization was found to proceed in conjunction with decarboxylation and with the loss of two hydrogen atoms to give fully aromatized heterocyclic bases. N-Formyl-*dl*-tryptophan in the presence of polyphosphoric acid *and* phosphorus oxychloride reacted to

form β-carboline in 35% yield, while N-acetyl-*dl*-tryptophan and N-acetyl-*dl*-phenylalanine under the same conditions gave 1-methyl-β-carboline and 1-methylisoquinoline, respectively, in lower yields. In no case could intermediates be isolated. The exact course by which the products were obtained has not been fully elucidated, but evidence has been presented to show that cyclization is probably the first step and that the loss of the two hydrogen atoms cannot be regarded as a simple oxidation.

As an introduction to a proposed program of study of the reactions of 1-amino-β-carboline, 1-aminoisoquinoline has been condensed with diethyl malonate to give 1,3-diketo-1,2,3,11-tetrahydro-4,11-diazaphenanthrene.

Preliminary experiments undertaken to develop a convenient synthesis of tryptamine from the readily available gramine or *dl*-tryptophan have shown that good yields of 3-indoleacetonitrile cannot be isolated from the alkylation of sodium cyanide with gramine, nor can N-formyltryptamine be obtained by the decarboxylation of N-formyl-*dl*-tryptophan.

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II. POLYPHOSPHORIC ACID AS A DEHYDRATING AGENT IN ORGANIC CHEMISTRY

Introduction

The essential step in a countless number of organic reactions is the elimination of the elements of water. These

processes lead to the formation of a great variety of products. In most of the reactions an acidic or basic catalyst is required, sometimes in only small amounts. Often, however, its function is more than catalytic and its presence is necessary in a quantity sufficient to cause it to act as one of the reagents participating in the reaction. Such materials in many instances are strongly acidic substances which either react with water or form stable hydrates, and thus effectively render unavailable the water formed in normally reversible processes. The present investigation was undertaken to determine whether polyphosphoric acid, an inhomogeneous material now manufactured commercially, could be used in reactions normally requiring the presence of such a dehydrating or condensing agent.

Discussion Of Results

The cyclodehydration of N-β-phenethylamides to 3,4-dihydroisoquinolines, commonly called the Bischler-Napieralski reaction, has been tested on N-formyl- and N-acetyl-β-phenethylamine. A 31% yield of 3,4-dihydroisoquinoline and a 23% yield of 1-methyl-3,4-dihydroisoquinoline, respectively, was obtained. Previously reported yields of 3,4-dihydroisoquinoline (1,2) have varied from 0 to 18%, while N-acetyl-β-phenethylamine has been cyclized in yields of 11 to 83% (3,2).

o-Benzoylbenzoic acid reacts to form anthraquinone quantitatively. *o*-(α-Naphthoyl)-benzoic acid is cyclized to naphthanthraquinnone in 44% yield. A procedure has been developed for the preparation of α-hydrindone by direct cyclization of hydrocinnamic acid in which a yield of the crude ketone of 62% is obtainable, while 35% of the starting material can be recovered ready for reuse. This method has been extended to the cyclization of 2-bromo-5-methoxy-hydrocinnamic acid. Experiments on the cyclodehydration of γ-phenylbutyric acid to α-tetralone remain inconclusive.

The acylation of mesitylene with acetic acid gave 30% of acetomesitylene in addition to 5-10% of a crystalline hydro-

carbon whose constitution has not been elucidated.

The dehydration of methylisobutyl carbinol and of 2-pentanol gave only small amounts of the corresponding olefins, most of which appeared to have undergone polymerization in the course of reaction, since higher-boiling mixtures were obtained.

In an attempted use of polyphosphoric acid as a solvent in the Skraup reaction to prepare 6-nitroquinoline from p-nitroaniline and glycerol, the amino compound was recovered. Similarly, no perinaphthenone was obtained when glycerol was allowed to react with β-naphthol; the use of both hydrogen fluoride and sulfuric acid as condensing agents in this reaction has been reported (4,5). An attempted Beckmann rearrangement of cyclohexanone oxime to ϵ-aminocaproic acid gave a highly impure product.

The self-condensation of acetone was investigated with a view to the preparation of mesitylene, but no advantage over the method which utilizes sulfuric acid (6) was found. Comparatively large amounts of other high-boiling condensation products could be obtained, however.

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VITA

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